

Remarks

Claims 1-6, 11-13, 16-19, 28-31, and 33-36 were pending in the subject application. Applicants gratefully acknowledge the Examiner's withdrawal of the previous rejections under 35 USC §103. Submitted herewith is a Request for Continued Examination (RCE) under 37 CFR §1.114 for the subject application. Applicants are requesting a 3-month suspension of action, as indicated on the attached RCE. By this Amendment, claims 1 and 28 have been amended and new claims 37 and 38 have been added. Support for the new claims and amendments can be found throughout the subject specification and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1-6, 11-13, 16-19, 28-31, and 33-38 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

Claims 1 and 28 are objected to on the grounds that they lack clarity. Applicants respectfully submit that the claims do not lack clarity. However, Applicants have amended claims 1 and 28 to clarify that the gene switch/biosensor is operatively linked to a promoter. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claims 1-6, 11-13, 16-19, 28-31, and 33-36 are rejected under 35 USC §103(a) as obvious over Tang *et al.* (2002) in view of Turgeman *et al.* (2001), Juan *et al.* (2001), and Nathwani *et al.* (2000). The Tang *et al.*, Turgeman *et al.*, and Juan *et al.* references are all cited for the teachings as described in the previous Office Actions. The Nathwani *et al.* reference is cited as teaching various viral vectors used for transducing human cells and the properties of recombinant AAV (rAAV) vectors that make them attractive for hematopoietic stem cell (HSC) transduction and transduction of CD34+ cells from umbilical cord blood. The Examiner concludes that it would have been obvious to combine the teachings of the cited references to arrive at Applicants' claimed invention. Applicants respectfully traverse these grounds for rejection.

Applicants respectfully assert that the cited references, taken alone or in combination, do not teach or suggest the claimed invention. As an initial matter, Applicants respectfully assert that the comments and arguments submitted in their Amendment dated September 29, 2010 were not directed to a method or to an "intended use" of a product as suggested by the Examiner in the instant

Office Action. Rather, Applicants' comments were directed to why it would not have been obvious to prepare or produce the claimed invention, *i.e.*, the cell of claim 1 or the tissue of claim 28, from the teachings of the cited references. In addition, Applicants respectfully assert that the arguments submitted in their Amendment of September 29, 2010 were not directed to "attacking references individually" as suggested by the Examiner in the instant Office Action. Rather, Applicants' comments were directed to the combined teachings of the cited references. Applicants note, however, that certain teachings of the cited references can only be discussed individually in Applicants' arguments, just as the Examiner discusses the references individually in the Office Action (see, for example, page 7 of the Office Action, where only the Tang *et al.* reference is discussed, or the paragraph bridging pages 8-9 of the Office Action, where only the Turgeman *et al.* reference is discussed).

Applicants maintain that there was no reason for an ordinarily skilled artisan, and no suggestion or motivation in the art at the time of the invention, to make or prepare genetically modified stem or progenitor cells comprising a gene switch/biosensor encoding a physiological stimulus-sensitive transactivator and a nucleic acid sequence encoding a heme oxygenase-1 (HO-1) product. The Office Action appears to suggest that transfection of any DNA of interest into any cell of interest is *prima facie* obvious. Under such a rationale, the Patent Office considers Applicants' claimed invention to be obvious because preparing a claimed cell might involve transfection of DNA into a cell of interest. Applicants respectfully disagree and submit that an ordinarily skilled artisan must have a reason for preparing all of the elements of the claimed invention or there must be a suggestion or motivation in the art to prepare all of the elements of the claimed invention.

The reason or motivation asserted by the Examiner for combining the vector of Tang *et al.* (which, according to the Examiner, can turn on gene expression in response to a hypoxic signal) in a hMSC is that "Turgeman *et al.* specifically teaches that genetically engineered hMSC displayed enhanced proliferation and osteogenic differentiation in culture; in vivo, transplanted genetically engineered hMSCs were able to engraft and form bone and cartilage in ectopic sites, and regenerate bone defects (non-union fractures) in mice radius bond; and importantly, the same results were obtained with hMSCs isolated from a patient suffering from osteoporosis..." (see page 18 of the Office Action). However, Applicants assert that the Turgeman *et al.* reference is concerned with the

ability of the hMSC to engraft and form bone and cartilage and regenerate bone defects. Applicants respectfully submit that Turgeman *et al.*'s teachings concerning bone and cartilage formation are irrelevant to Applicants' claimed invention wherein the genetically modified cells comprise a nucleic acid sequence encoding HO-1 that is expressed to help the cells survive in low oxygen conditions. HO-1 catalyzes the degradation of heme and, thus, is not relevant to bone or cartilage formation.

Moreover, there is no apparent reason for a skilled artisan, and no suggestion or motivation provided by the cited references, to specifically substitute a nucleic acid encoding HO-1 for the reporter gene in the vector of the Tang *et al.* reference. Again, Applicants note that it was not known in the art at the time of Applicants' invention that stem cells implanted in ischemic tissue had a high death rate. Thus, there would have been no reason to genetically modify stem cells to incorporate and express HO-1 since it was not known that there might be a need for stem cells to express HO-1 as a "therapeutic" protein. As noted herein, the Turgeman *et al.* reference pertains only to modified hMSC for bone and/or cartilage formation. The Tang *et al.*, Turgeman *et al.*, and Juan *et al.* references do not teach or suggest anything concerning modifying a stem cell to express a gene encoding an enzyme that is useful in helping the stem cell survive in low oxygen conditions.

Applicants again note that the authors of the Tang *et al.* reference did not teach or suggest an approach for improving stem cell survival when the cells are transplanted into injured tissue, such as ischemic heart tissue. The work reported in the Tang *et al.* reference is directed solely to development of an injectable gene switch which would reside in specific body tissue, such as heart ventricle, defined by the promoter incorporated into the gene switch. The Tang *et al.* reference does not teach or suggest anything concerning stem cell transplantation and a skilled artisan would not have looked to combine the teachings of Turgeman *et al.* with those of the Tang *et al.* reference. Thus, a person of ordinary skill in the art would not have looked to the Tang *et al.* reference for teachings relevant to the preparation of Applicants' claimed invention.

Applicants also respectfully maintain that it is only the present invention that solved the problem of poor cell survival that occurs in stem cell therapy. It is well settled in U.S. patent law that a patentable invention may lie in the discovery of a source of a problem. *Eibel Process Co. v. Minnesota & Ontario Paper Co.*, 261 US 45 (1923); *In re Spinnoble*, 160 USPQ 237 (CCPA 1969). None of the cited references, including the secondary references, teach or suggest anything of

relevance in regard to the problem of implanted stem cell survival, *i.e.*, that stem cells in ischemic tissue had a high death rate. Thus, a person of ordinary skill in the art would not have been motivated or had an apparent reason to combine the exogenous first and second polynucleotide of the subject invention into a stem cell or a progenitor cell.

Applicants also take note of the Examiner's comments regarding the U.S. Supreme Court decision in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). Applicants respectfully submit that they did not indicate that a specific teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. Rather, Applicants indicated that generally a suggestion must be found, along with a reasonable expectation of success. Moreover, Applicants explicitly cited the *KSR* decision in their September 29 Amendment for the proposition that a combination of elements is not *prima facie* obvious if an ordinarily skilled artisan would not have recognized an apparent reason to combine the elements. Applicants respectfully maintain that there was no apparent reason to an ordinarily skilled artisan to combine the elements of the cited references because, as noted above, the high rate of death of implanted stem cells in an ischemic tissue environment was not known in the art at the time of the invention. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §103(a) is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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Attachment: Request for Continued Examination